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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,659	08/31/2001	Gregory R. Mundy	A061CIP1	2421

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,659	MUNDY ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 17-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12/02 &10/03*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-50 are pending.

2. Applicant's election with traverse of Group V, claims 12-16 a method of treating multiple myeloma with alpha4-specific antibodies and a second composition comprising a compound filed on 11/5/03, is acknowledged.

Applicant's traversal is on the grounds that the preambles of Groups V, XIII and XXI read on overlapping subject matter and thus should be grouped together. Further, Groups V, VIII and XXI share the same class and subclass, read on overlapping subject matter and thus should be grouped together. Furthermore, the Examiner has not established that a serious burden would be involved in searching those Groups. This is not found persuasive because the method of treating multiple myeloma, the method of inhibiting bone resorption associated with tumors of bone marrow and the method of treating a subject having a disorder characterized by the presence of osteoclastogenesis differ in etiologies and therapeutic endpoints; thus each condition represents patentably distinct subject matter. Further, applicant admits that 20% of patients with MM do not suffer for devastating osteolytic bone destruction caused by increased osteoclast formation and activity. Thus, a reference against Group XIII is not necessarily a reference against Groups V and XXI. Therefore, each method is patentably distinct and are recognized divergent subject matter. Further, presence of osteoclastogenesis is associated with various pathogenesis such as Crohn's disease. Therefore, searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group.

the pathological conditions differ in etiologies and therapeutic endpoints; thus each condition represents patentably distinct subject matter

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-11 and 17-50 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 12-16 are under examination as they read on method of treating multiple myeloma/inhibiting bone resorption associated with tumors of bone marrow with alpha4-specific antibodies and a second composition comprising a compound.

5. Applicant's IDS, filed 12/5/01 and 10/20/03, is acknowledged, however, abstracts A2 and A4, filed on 12/5/01, were crossed out as the both abstract are duplicates of the abstracts presented in references A3 and A5, respectively.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 is indefinite in the recitation "than not administered in combination with said second composition" lines 4-5 and lines 8-10 and the recitation "said second composition" line 10. Claim 16 depends from claim 12 which claim the combination of both antagonist and a second composition, it is unclear how the antagonist would be administered in the absent of the second composition. Further, the compound is encompassed by the second composition. Thus, it is unclear how the compound is lower in the absent of itself. Finally, the recitation "or both" on line 11, is indefinite because it is unclear how antagonist can be lower and higher at the same time.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating multiple myeloma comprising with alpha4-specific antibodies and a second composition comprising a melphalan, a bisphosponate, thalidomide or erythropoiention, does not reasonably provide enablement for any method for treating multiple myeloma comprising administering to an individual a therapeutically effective amount of a first composition comprising any "antagonist of an interaction between an α4 subunit-bearing integrin and a ligand for an α4 subunit-bearing integrin" wherein said first composition is administered in combination with a therapeutically effective amount of a second composition comprising any "compound" that is not an antagonist of an interaction between an α4 subunit-bearing integrin and a ligand for an α4 subunit-bearing integrin in claim 12, wherein said compound is any chemotherapeutic agent in claim 13, wherein said chemotherapeutic agent is any antagonist of IL6 and any antagonist of IL15 in claim 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification dose not provide a sufficient enabling description of the claimed invention.

There is insufficient guidance and direction as how to make and use any antagonist of an interaction between an α4 subunit-bearing integrin and a ligand for an α4 subunit-bearing integrin, any second composition comprising any compound that is not an antagonist of an interaction between an α4 subunit-bearing integrin and a ligand for an α4 subunit-bearing

integrin, any chemotherapeutic agent such as any antagonist of IL6 and any antagonist of IL15. or a method for inhibiting bone resorpation associated with tumors of bone marrow.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only the antibodies against α4 as α4 antagonist and a melphalan, a bisphosponate, thalidomide and erythropoiention as chemotherapeutic agent. A person of skill in the art is not enabled to make and use "an antagonist" and "a compound" as recited in claims. A person of skill in the art would not know which antagonists or compounds are essential to treat MM. Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-termianl sequence, etc.) that distinctly identifies such "antagonist" for α4 and a "compound" such as chemotherapeutic agents such as antagonist for IL6 or IL15.

It is well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Applicant has not enabled structurally related and unrelated compounds comprising any antagonist of an interaction between an α4 subunit-bearing integrin and a ligand for an α4 subunit-bearing integrin for treating MM, or any compound that is not an antagonist of an interaction between an α4 subunit-bearing integrin and a ligand for an α4 subunit-bearing integrin. These compounds and antagonists would be expected to have greater differences in their activities. Reasonable correlation must exist between the scope of the claims and the scope of the enablement set forth.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 12-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method of treating multiple myeloma comprising with alpha4-specific antibodies and a second composition comprising a melphalan, a bisphosponate, thalidomide or erythropoiention.

Applicant is not in possession of any method for treating multiple myeloma comprising administering to an individual a therapeutically effective amount of a first composition

comprising any "antagonist of an interaction between an α4 subunit-bearing integrin and a ligand for an α4 subunit-bearing integrin" wherein said first composition is administered in combination with a therapeutically effective amount of a second composition comprising any "compound" that is not an antagonist of an interaction between an α4 subunit-bearing integrin and a ligand for an α4 subunit-bearing integrin in claim 12, wherein said compound is any chemotherapeutic agent in claim 13, wherein said chemotherapeutic agent is any antagonist of IL6 and any antagonist of IL15 in claim 14.

Applicant has disclosed only anti-α4 antibodies and melphalan, a bisphosphonate, thalidomide and erythropoietin; therefore, the skilled artisan cannot envision all the contemplated antagonist, agent and compound possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The filing date of the instant claims is deemed to be the filing date of the instant applications, i.e., 08/31/2001, as the parent application is drawn only to the administration of anti-α4 antibody, and thus does not support the claimed limitations of the instant application of a combined administration of mephalan and anti-α4 antibody.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 12-16are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Zaanen et al (Br. J. Haematol. 102:783-90, August 1998) in view of Masellis-Smith et al (IDS Ref No. A1 and Lokhorst et al (Blood 84:2269-2277, 1994) and U.S. Patent No. 5,885,786 or Alexanian et al (JAM, 208:1680-1685, 1969).

Van Zaanen et al teach a method for treating multiple myeloma comprising administering chimaeric monoclonal anti-IL-6 antibodies (cMab) in multiple myeloma patients, the cMab was given in a dosage of 5-40 mg/d (see the entire document and the abstract on page 783 in particular).

The Van Zaanen *et al* teaching differs from the claimed invention by not expressly disclosing to employ an antagonist of an interaction between an α4 subunit-bearing integrin and a ligand for an α4 subunit-bearing integrin in combination with a therapeutically effective amount of a second composition comprising a compound that is not an antagonist of an interaction between an a4 subunit-bearing integrin and a ligand for an α4 subunit-bearing integrin in claim 12, wherein the compound is a chemotherapeutic agent in claim 13, wherein the chemotherapeutic agent is melphalan in claims in 14 and 15, wherein to be thereapeutically effective, a dosage of said antiagonist is lower when administered in combination with said second composition than not administered in combination with said second composition; or a dosage of said compound is lower when administered in combination with said first composition than not administered in combination with said second composition, or both in claim 16

Masellis-Smith *et al* teach function-blocking monoclonal antibodies such as mAbs against very late antigen 4 that inhibit the CD19+ multiple myelom blood B cell interaction with BM fibroblasts. Furthermore, Masellis-Smith *et al* teach that the alpha4beta7 ligand is mediated MM blood B cell adhesion (see the entire document and abstract page 930 in particular).

Lokhorst *et a*l teach monoclonal antibodies directed to the α4-integrin (VLA-4) that inhibit binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma. Furthermore, the antibodies to VLA-4 inhibited the induced IL-6

secreation. Furthermore, Lokhorst *et al* teach that the intimate cell-cell contact is a prerequisite for IL-6 induction and the physical separation of plasma cells and LTBMC by mechanical means such as monoclonal antibodies to VLA-4 which is involved in the adhesion process, inhibit the induction of IL-6 production by LTBMC. (entire document and abstract page 2269, and page 2276, left column 2nd paragraph in particular).

The '786 patent teaches that melphalan is available in tablet form for oral administration and has been used to treat multiple myeloma. Further, the `786 patent teaches that available evidence suggests that about one third to one half of the patients with multiple myeloma show a favorable response to oral administration of the drug (see col., 29 under Melphalan in particular).

Alexanian et al teach a method of treating multiple myeloma using a combination therapy with melphalan and perdnisone melphalan with a higher response rate in comparison with melphalan alone (see abstract in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody taught by the Van Zaanen *et al* with the antibody that specifically binds the α4 integrin taught by Masellis-Smith *et al* or Lokhorst *et al.*, and combined the anti-α4 antibody with melphalan as taught by the `786 patent or Alexanian *et al* in a method of treating multiple myeloma (MM).

One of ordinary skill in the art at the time the invention was made would have been motivated to subsitute the anti-IL-6 antibodies with anti-α4 antibodies in a method of treating MM because antibodies against alpha4 integrin inhibit cell-cell contact which is a prerequisite for IL-6 induction as taught by Lokhorst *et al* and because antibodies against alpha4 integrin inhibit the adhesion of alpha4beta7 integrin of B cells from MM patients with its ligand on the bone marrow (BM) fibroblast and hence prevent extravasation into the BM. Further, melphalan is currently used in the treatment of multiple myeloma and available evidence suggests that about one third to one half of the patients with multiple myeloma show a favorable response to oral administration of the drug as taught by the `786 patent. In addition, the combination therapy with melphalan melphalan provides a higher response rate in comparison with melphalan alone as taught by Alexanian *et al* reference. Moreover, the motivation to combine the anti-α4 antibody with melphalan can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose (i.e., treating MM). Section MPEP 2144.07.

Claim 16 is included because the determination of the optimal dosage of treatment is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
January 22, 2004

Christina Chan

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